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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/042,488	03/16/1998	RONALD M. EVANS	SALK1520-2	5034

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EXAMINER

KAUSHAL, SUMESH

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 02/11/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/042,488

Applicant(s)

EVANS ET AL.

Examiner

Sumesh Kaushal Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 January 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-9,11-13,15-24,39,40,47-55 and 57-77 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) 71 is/are allowed.
- 6) ☐ Claim(s) 1,3-9,11-13,15-24,39,40,47-55,57-70 and 72-77 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/13/03 has been entered.

Claims 1, 3-9, 11-13, 15-24, 39-40, 47-55 and 57-77 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (<http://www.uspto.gov>) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.*

Claim Rejections - 35 USC § 112

Claims 1, 3-9, 11-13, 15-24, 39-40, 47-55, 57-70 and 72-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

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specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention** for the same reasons of record as set forth in the office action mailed on 08/13/02.

The applicant argues that each component contemplated for use in the present invention is explicitly disclosed in the specification. Thus one skill in the art would have no reason to doubt that applicants were in the possession of the claimed invention at the time of filing (response, page 16 para.1).

However, this is found NOT persuasive because applicant's argument alone cannot take place of evidence lacking in the record (see *In re Scarbrough* 182 USPQ, (CCPA) 1979). A single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L. P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000). *At best the specification as filed only discloses a modified ecdysone receptor (VgEcR) which in combination with hybrid responsive element E/GRE enables the method as claimed wherein the response element has no binding affinity for FXR receptor (spec. Fig-1B)*. Even though the applicant argues that each component contemplated for use in the present invention is explicitly disclosed in the specification, besides the hybrid responsive element E/GRE there is no description of other response elements that bind to the modified ecdysone receptor. Similarly besides the modified ecdysone receptor VgEcR the instant specification fails to disclose any other modified receptor that mediates the transactivation of an exogenous gene operatively linked to any other response element wherein the response element has no binding affinity for FXR. Furthermore, there is no description how the structure of *Drosophila* ecdysone receptor

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relates to the structure of any naturally occurring ecdysone receptors. The general knowledge in the art concerning ecdysone receptor does not provide any indication as how the structure of *Drosophila* ecdysone receptor and response element is representative of other unknown homologs having concordant or discordant functions (see NO et al, PNAS 93:3346-3351, 1996, ref. of record). At best the specification only disclosed ecdysteroid-induced responsiveness in a modified ecdysone receptor system comprising VgEcR (*Drosophila*) and E/GRE response element that has substantially no binding affinity for farnesoid-X-receptor.

The state of the art at the time of filing was such that the ecdysone hormone responsiveness is mediated by the functional ecdysone response complex, a heterodimer of the insect ecdysone receptor (EcR) either with its natural dimeric partner, the ultraspiracle gene product (USP) or with the retinoid X receptor (RXR) a mammalian homolog of USP (Hoppe et al Mol. Ther. 1(2):159-164, 2000). The functional ecdysone receptor is composed of a heterodimer between the ecdysone-binding receptor (EcR) and a RXR homologue, the EcR/RXR complexes repress the transcription in the absence of ligand and recruit coactivators in the presence of the ligand in ecdysone receptor system (Ghbeish et al, PNAS98(7):3867-3872, 2001). However, no mammalian transcription factors have been shown to have a natural enhancer element like the EcRE, which is composed of two inverted half-sites of the sequence AGGTCA spaced by 1 nucleotide and it is difficult to preclude such a possibility (NO et al, PNAS 93:3346-3351, 1996, page 3349, col.1 para.2). In addition the art at the time of filing further teaches that farnesoid X receptor (FXR) can activate certain synthetic promoters containing an EcRE response element in response to farnesoids. Only the modified ecdysone receptor VgEcR containing mutation in 3 amino acid residues render the modified receptor

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responsive to a hybrid responsive element called the E/GRE (ecdysone/glucocorticoid response element). Although FXR can activate a promoter containing the wild type EcRE, it cannot activate one containing the E/GRE. (NO et al, page 3349, col.1 para.2). Considering the applicant's disclosure and the state of art, one skill in the art would have reasons to doubt that applicants were in the possession of the claimed invention at the time of filing.

Furthermore, the possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991). In claims to genetic material, generic statement such as "vertebrate insulin cDNA" or mammalian insulin cDNA," without more, is not adequate written description of claimed genus, since it does not distinguish genus from others except by function, and does not specifically define any of genes that fall within its definition, or describe structural features commonly possessed by members of genus that distinguish them from others; accordingly, naming type of material generally known to exist, in absence of knowledge as to what that material consists of, is not description of that material (*Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406). In the instant case the response element as claimed (any and all) has been defined only by a statement of function to which a modified ecdysone receptor binds. Similarly, a DNA-binding domain as claimed (any and all) has been defined as a domain that binds to a response element (any and all). In addition,

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a modified receptor as claimed (any and all) has been defined that binds to an ecdysone response element which conveyed no distinguishing information about the identity of the claimed response elements, DNA-binding domains, modified receptors and silent partners, such as its relevant structural or physical characteristics. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

Claims 1, 3-9, 11-13, 15-24, 39-40, 47-55, 57-70 and 72-77 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the expression of an exogenous gene in an isolated cell containing i) a DNA construct comprising the exogenous gene under the control of the disclosed modified ecdysone response element E/GRE wherein the response element has substantially no binding affinity for farnesoid-X-receptor (FXR), and ii) a modified ecdysone receptor (VgEcR) which in the presence of an exogenous ecdysteroid and in the presence of EcR silent partner (RXR) bind to the ecdysone response element (E/GRE), does not reasonably provide enablement for the method as claimed wherein an isolated cell comprising a) a response element (other than E/GRE) that has substantially no binding affinity for FXR and b) a modified receptor and/or their silent partners (other than one found in the ecdysone receptor system) that contain a ligand binding domain (other than the ecdysone ligand binding domain) and a DNA binding domain (other than one binds to the ecdysone response element). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use

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the invention commensurate in scope with these claims for the same reasons of record as set forth in the office action mailed on 08/13/02.

Nature Of Invention:

The instant invention is drawn to a method of modulating an expression of an exogenous gene in an isolated cell or in a mammalian subject (gene therapy) containing a genetically modified receptor and DNA construct comprising an exogenous gene under the control of a response element, wherein the binding of a ligand to the receptor results in the modulation of an exogenous gene of interest operably linked to the response element.

Breadth Of Claims And Guidance Provided By The Inventor.

The scope of instant claims encompass a method for modulating the expression of an exogenous gene in an isolated cell or in a mammalian subject (claims 72-77) that require a) a response element (other than E/GRE) that has substantially no binding affinity for FXR and b) a modified receptor and/or their silent partners (other than as found in ecdysone receptor system) that contain a ligand binding domain (other than ecdysone ligand binding domain) and a DNA binding domain (other than one that binds to ecdysone response element). At best the specification as filed only discloses a modified ecdysone receptor (VgEcR) which in combination with hybrid responsive element E/GRE enables the method as claimed wherein the response element has no binding affinity for FXR receptor (spec. Fig-1B). In addition the specification only teaches ecdysone responsiveness in a cell line (293) **in-vitro** via transient transfection of a modified ecdysone receptor VgEcR, a heterodimeric partner (RXR) and an ecdysone inducible reporter gene (example-3), which does not represent the modulation of the expression of an exogenous gene in a mammalian subject

State Of Art And Predictability

The state of the art at the time of filing was such that the ecdysone hormone responsiveness is mediated by the functional ecdysone response complex, a heterodimer of the insect ecdysone receptor (EcR) either with its natural dimeric partner, the ultraspiracle gene product (USP) or with the retinoid X receptor (RXR), a mammalian homolog of USP (Hoppe et al Mol. Ther. 1(2):159-164, 2000). Similarly, the retinoic acid receptor and the thyroid hormone receptor require dimerization with a second nuclear receptor, the retinoid X receptor. The functional ecdysone receptor is composed of a heterodimer between the ecdysone-binding receptor (EcR) and a RXR homologue, the EcR/RXR complexes repress the transcription in the absence of ligand and recruit coactivators in the presence of the ligand in ecdysone receptor system (Ghbeish et al, PNAS98(7):3867-3872, 2001). However, no mammalian transcription factors have been shown to have a natural enhancer element like the EcRE, which is composed of two inverted half-sites of the sequence AGGTCA spaced by 1 nucleotide and it is difficult to preclude such a possibility (NO et al, PNAS 93:3346-3351, 1996, page 3349, col.1 para.2). The art at the time of filing teaches that farnesoid X receptor (FXR) can activate certain synthetic promoters containing an EcRE response element in response to farnesoids. The modified ecdysone receptor VgEcR containing mutation in 3 amino acid residues render the modified receptor responsive to a hybrid responsive element called the E/GRE (ecdysone/glucocorticoid response element). Although FXR can activate a promoter containing the wild type EcRE, it cannot activate one containing the E/GRE. Similarly, the E/GRE linked reporter gene is not activated by GR nor does VgEcR activate a dexamethasone responsive promoter (NO et al, page 3349, col.1 para.2). Therefore considering the complexities in the ecdysone responsive systems

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especially in view of farnesoid X receptor system and the amount of guidance provide in the specification, the method as claimed is highly unpredictable for an uncharacterized inducible receptor system as claimed.

In addition, Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996, ref of record). Even though the invention as claimed does not require any therapeutic effects, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). Even though, the gene bases therapies holds much promise to come, the success will only be achieved through continued rigorous research on the

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most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals

Quantity Of Experimentation Required

The applicant argues that the specification as filed enables any person skilled in the art to make and use the invention commensurate with the present claims. The applicant further argues that methods for creating DNA constructs encoding the contemplated receptor(s) and an exogenous gene to be regulated and for transfecting cells with these constructs are standard routine molecular biological manipulations clearly known to one skill in the art at the time of filing (*response, page 17-8*).

However, this is not found persuasive because applicant's argument alone cannot take place of evidence lacking in the record. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). The scope of instant claims encompass a method for modulating the expression of an exogenous gene in an isolated cell or in a mammalian subject (claims 72-77) that requires a) a response element (other than E/GRE) that has substantially no binding affinity for FXR and b) a modified receptor and/or their silent partners (other than as found in the ecdysone receptor system) that contain a ligand binding domain (other than the ecdysone ligand binding domain) and a DNA binding domain (other than one binds to the ecdysone response element). At best the specification as filed only discloses a modified ecdysone receptor (VgEcR) which in combination with hybrid responsive element E/GRE enables the method as claimed wherein the response element has no binding affinity for FXR receptor (spec. Fig-1B).

It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), *Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In the instant case applicant was not in the possession of the claimed genus, since description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim (*supra W.D. issues*). The response element as claimed (any and all) has been defined only by a statement of function to which a modified ecdysone receptor binds. Similarly, a DNA-binding domain as claimed (any and all) has been defined as a domain that binds to a response element (any and all). Furthermore, a modified receptor as claimed (any and all) has been defined that binds to an ecdysone response element which conveyed no distinguishing information about the identity of the claimed response elements, DNA-binding domains and modified receptors, such as its relevant structural or physical characteristics.

The courts have clearly stated that: "A specification need not to disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement

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requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. *It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement*". Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997). In instant case the specification fail to meet the enablement requirement, since there is no disclosure of the specific material required to make and use the invention commensurate in scope with instant claims.

In addition, the invention as claimed encompasses a method for modulating the expression of an exogenous gene in-vivo (a mammalian subject). The method requires the successful expression of the modified receptor and corresponding response element linked to an exogenous gene with in same cell in vivo. Considering the unpredictability in the state of gene therapy art the specification even fails to disclose a single working example wherein expression of an exogenous gene of interest has been achieved by transducing the disclosed "ecdysone inducible system" into a mammalian subject. The invention as claimed clearly requires the presence of both receptor and response element components in a single cell. Since, the presence of an ecdysone inducible system in a single cell in a mammalian subject is the prerequisite of instant invention, it is not clear how one skilled in the art would use the invention as claimed without any reasonable expectation of success in view of instant disclosure.

Considering the unpredictability in the state of art the specification as filed fails to disclose a) a response element (other than the E/GRE) that has substantially no binding affinity

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for FXR and b) a modified receptor and/or their silent partners (other than one found in the ecdysone receptor system) that contain a ligand binding domain (other than the ecdysone ligand binding domain) and a DNA binding domain (other than one binds to the ecdysone response element). In addition considering the unpredictability in the gene delivery art, the specification fails to disclose a single working example wherein expression of an exogenous gene has been modulated by transducing any inducible system (as claimed) into a mammalian subject. *Since the modulation of gene expression using a modified receptor containing an uncharacterized DNA-binding domain that binds to an uncharacterized response element (as claimed) is not considered routine in the art without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.* See *In re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. The undue experimentation required would include structural and functional characterization of a) a response element (other than the E/GRE) that has substantially no binding affinity for FXR and b) a modified receptor and/or their silent partners (other than one found in the ecdysone receptor system) that contain a ligand binding domain (other than the ecdysone ligand binding domain) and a DNA binding domain (other than one binds to the ecdysone response element). In addition the undue experimentation required would include delivery of both modified receptor and response element constructs into a single cell in a

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mammalian subject and subsequent modulation of the transduced inducible system using the ligand required.

Conclusion

Claims 1, 3-9, 11-13, 15-24, 39-40, 47-55, 57-70 and 72-77 stand rejected.

Claim 71 is allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 703-305-6838. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-8724 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

S. Kaushal
PATENT EXAMINER


JEFFREY FREDMAN
PRIMARY EXAMINER